HED DOC. NO. 013401

DATE: May 26, 1999

MEMORANDUM

SUBJECT: ***PIRIMIPHOS METHYL*** **- REPLACEMENT OF HUMAN STUDY USED IN RISK ASSESSMENTS -** Report of the Hazard Identification Assessment Review Committee.

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and
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On February 11, 1999, the Health Effect Division's (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the toxicology database for pirimiphos methyl and selected doses and toxicology endpoints for risk assessment, based solely on **animal toxicity studies**. The HIARC also determined the appropriate uncertainty factors and margins of exposures for dietary and non-dietary risk assessments. **For clarity, transparency, and utility, the decisions made at the previous HIARC meetings along with those made at this meeting are presented in this report. Consequently, the information contained in this report should be used for risk assessments and supersedes all other reports (RfD, TES, HIARC, etc) for pirimiphos methyl.**

Committee Members in Attendance

Members present were: David Anderson, William Burnam, Virginia Dobozy, Pam Hurley, Mike Ioannou, Tina Levine, Nicole Paquette, Kathleen Raffaele, Jess Rowland, Brenda Tarplee (Executive Secretary), and Pauline Wagner. Member in absentia: Susan Makris and PV Shah

Other HED staff present at the meeting were: Paul Chin, William Sette, and Sanju Diwan**.**

Brenda Tarplee
Executive Secretary
Hazard Identification Assessment Review Committee

I. BACKGROUND

On January 12, 1998, the Health Effects Division's (HED) Hazard Identification Assessment Review committee (HIARC) evaluated the toxicology data base, selected doses and endpoints for acute dietary as well as occupational and residential exposure risk assessments, re-assessed the Reference Dose (RfD) established for chronic dietary risk assessment, and addressed the sensitivity of infants and children from exposure to Pirimiphos-methyl as required by the Food Quality Protection Act (FQPA) of 1996 (HIARC Report dated January 29, 1998; HED Document No. 012465).

In December 10-11, 1998, the Science Advisory Board/Scientific Advisory Panel discussed both the ethical concerns and the scientific merit of using humans subjects for testing pesticides. The Agency is currently developing a policy for the use of human studies in risk assessment. In the interim, HED has taken the following course of action.

In January, 1999, the HIARC developed a specific outline of parameters and questions for the re-examination of human studies. Human studies were used in endpoint selection for risk assessment for eight organophosphates, including pirimiphos methyl. These studies were re-evaluated according to the parameters and questions developed by the Committee. The HIARC then selected doses and endpoints from toxicity studies with animals for each of these eight organophosphate. The HIARC examined the human data in conjunction with the animal data to determine the appropriate inter-species uncertainty factor.

In the evaluation of the comparative toxicology data in laboratory animals and humans, when the data were suitable for comparison, the Committee relied mainly on the LOAEL for cholinesterase inhibition at comparable time points (duration). The comparative data were evaluated as follows:

> If the comparative data indicate (by the dose level and the magnitude of the effect) that humans are more sensitive than laboratory animals, there is no justification for reducing the 10x inter-species uncertainty factor.
>
> If the comparative data indicate (by the dose level and the magnitude of the effect) that humans and laboratory animals are equally sensitive or that humans are less sensitive than laboratory animals, consideration was given to reducing the inter-species uncertainty factor.

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On January 14, 1999, using the parameters developed for evaluation of the human studies, the HIARC evaluated the 28 day oral study (Chart et al., 1974; MRID Nos. 00097671) and the 56-day oral study (Howard and Gore, 1976; MRID No. 000807-32) in humans with pirimiphos methyl. The HIARC classified these studies as *supplemental* because the results provided useful scientific information that can be used as supportive data along with the results from the animal studies, but the studies alone are not sufficient for endpoint selection or risk assessments due to technical limitations.

On February 11, 1999, HIARC evaluated the doses and toxicology endpoints selected for pirimiphos methyl based solely on animal toxicity studies The HIARC also determined the appropriate uncertainty factors and margins of exposures for dietary and non-dietary risk assessments.

For clarity, transparency, and utility, the decisions made at the previous HIARC meetings along with those made at this meeting are presented in this report. Consequently, the information contained in this report should be used for risk assessments.

II. HAZARD IDENTIFICATION

A. Acute Dietary Reference Dose (RfD)

Study Selected: Acute Neurotoxicity Study in the Rat §81-8

MRID No. 43594101

Executive Summary: In an acute neurotoxicity study, groups of Sprague-Dawley rats (17/sex/dose) received a single oral administration of pirimiphos methyl in corn oil at 0, 15, 150 or 1500 mg/kg. Assessments were made for Functional Observation Battery (FOB) and motor activity at pretest, 24 hours, 7 days and 14 days after dosing. Plasma and red blood cell cholinesterase activity was measured at the same intervals. Regional brain cholinesterase activity was measured 24 hours and 15 days after dosing and neuropathology was assessed 15 days after dosing. At 15 mg/kg after 24 hours, plasma cholinesterase inhibition (ChEI) was 48% in females and 21% in males (both $p<0.01$) and in males RBC ChEI was inhibited 26% ($p <0.01$) and midbrain ChEI was 10% ($p <0.05$). At 1500 mg/kg, brain ChEI persisted to day 15 with there being up to 30% inhibition. Alterations in FOB and Motor Activity were seen only at 1500 mg/kg (the highest dose tested) at 24 hours in both sexes. The LOAEL was 15 mg/kg based on the ChEI observed in plasma, RBC, and brain.

Dose and Endpoint for Risk Assessment: LOAEL=15 mg/kg based on inhibition of plasma (male and female) and RBC and brain cholinesterase activity (in males) after 24 hours.

Uncertainty Factor: 1000 (10x for intra-species variation, 10x for inter-species extrapolation, and 10x for the use of LOAEL as well as the severity of effects observed).

$$\textbf{Acute RfD} = \frac{\text{15 mg/kg/day (LOAEL)}}{\text{1000 (UF)}} = \textbf{0.015 mg/kg}$$

Comments about study, endpoint and UF: **This dose and endpoint replaces the previous dose/endpoint based on the human study.** The dose/endpoint/study is appropriate for this risk assessment because the effects were seen after a single exposure on Day 1. The UF includes the 10x for intra-species variation, 10x for inter-species extrapolation, and 10x for the use of LOAEL as well as the severity of effects (marked plasma as well as RBC and brain ChEI) seen at the lowest dose tested.

The HIARC concluded that the 10x inter-species uncertainty factor cannot be modified/altered. The 28-day study in humans (Chart *et al.* 1974) is useful only as *supplemental* data. Although this study is not appropriate for use in risk assessment, it did provide some evidence that humans may be more sensitive than animals since the effect level for cholinesterase inhibition in humans (0.25 mg/kg) is lower than the effect levels seen in repeated dose animal studies. In addition, the human study tested only a single dose in five male subjects and, although plasma and red blood cell cholinesterase activity were measured, the time of sampling varied from subject to subject. These types of data while providing a qualitative snapshot of time course vs. cholinesterase inhibition, are inadequate for quanitative purposes.

B. Chronic Dietary RfD

Study: Subchronic Toxicity-Rat §82-7

MRID No. 43608201

Executive Summary: In a subchronic neurotoxicity study, groups of Sprague-Dawley rats (10/sex/dose) were fed diets containing pirimiphos-methyl (89.8%) at dose levels of 0, 3, 30 or 300 ppm (0, 0.2, 2.1 or 21.1 for males and 0, 0.2, 2.4 or 24.7 mg/kg/day for females, respectively) for 90-days. Assessments for FOB and motor activity and measurements of plasma, red blood cell and brain cholinesterase activity were made at pretest, and at weeks 3, 7 and 13 post treatment. No systemic toxicity was seen. The systemic NOAEL was 24.7 mg/kg/day (HDT); a LOAEL was not established. For plasma ChEI, the NOAEL was <0.2 mg/kg/day (LDT) and the LOAEL was 0.2 mg/kg/day. For red blood cell ChEI, the threshold NOAEL/LOAEL was 2.1 mg/kg/day. For brain ChEI, the NOAEL was 2.1 mg/kg/day and the LOAEL was 21.1 mg/kg/day.

Dose and Endpoint for Risk Assessment: LOAEL=0.2 mg/kg based on plasma cholinesterase inhibition in males and females at the lowest dose tested.

Uncertainty Factor: 1000 (10x for intra-species variation, 10x for inter-species extrapolation, and 10x for the use of LOAEL/data gaps for long-term studies).

$$\textbf{Chronic RfD} = \frac{\text{0.2 mg/kg/day (NOAEL)}}{\text{1000 (UF)}} = \textbf{0.0002 mg/kg/day}$$

Comments about study, endpoint and UF: **This dose and endpoint replaces the previous dose/endpoint based on the human study.** The UF includes the 10x for inter-species extrapolation, 10x for intra-species variation, and 10x for the use of LOAEL as well as data gaps for chronic toxicity studies in rats and dogs. Although a 90-day study is used to establish the chronic RfD an additional uncertainty factor was not deemed necessary (for use of a study of shorter duration) since the principal effect (cholinesterase inhibition) demonstrated in the critical study (90-day study) is supported by the Week 3, 7, and 13 measurements in the long-term studies (i.e., two-generation reproduction study in rats and the carcinogenicity study in mice).

The HIARC concluded that the 10x inter-species extrapolation factor cannot be modified/altered. The 56-day study in humans (Howard *et al.* 1976) is useful only as *supplemental* data. Although this study used male and female subjects and provided supportive scientific data, it is not appropriate for use in risk assessment since it only included a single dose (thus no dose-response data) and only measured cholinesterase activity in subset of subjects. Additionally, steady-state was not achieved and the treatment regimen (56 days) is not adequate to characterize lifetime exposure. Therefore, no comparison of dose and effects in animals and human subjects could be made.

C. Occupational/Residential Exposure

1. Dermal Absorption

A dermal absorption factor is required since oral values were selected for Short-, Intermediate-, and Long-term dermal risk assessments. The Committee concluded that a 100% dermal absorption value is appropriate for pirimiphos-methyl. This decision is based upon the comparisons of LOAELs in the oral developmental toxicity (LOAEL = 24 mg/kg/day) and the 21-day dermal toxicity studies (LOAEL = 4 mg/kg/day) in rabbits based on the common endpoint (cholinesterase inhibition) (*Memorandum:* B. Tarplee and J. Rowland dated February 24, 1999; HED Document. 013270).

Dermal Absorption Factor: 100% (extrapolated)

2. Short-Term Dermal (1-7 days)

Study Selected: Acute Neurotoxicity Study in the Rat §81-8

MRID No. 43594101

Executive Summary: See Acute Dietary

Dose and Endpoint for Risk Assessment: LOAEL=15 mg/kg based on inhibition of plasma (male and female) and RBC and brain cholinesterase activity (in males) after 24 hours.

Comments about Study/Endpoint/MOE: **This dose and endpoint replaces the previous dose/endpoint based on the human study.** The HIARC determined that the 28-human study is useful only as *supplemental* data. Although this study is not appropriate for use in risk assessment, it did provided some evidence that humans may be more sensitive than animals since the effect level for cholinesterase inhibition in humans (0.25 mg/kg) is lower than the effect levels seen in repeated dose animal studies. In addition, the human study tested only a single dose in five male subjects and, although plasma and red blood cell cholinesterase activity were measured, the time of sampling varied from subject to subject. These types of data while providing a qualitative snapshot of time course vs. cholinesterase inhibition, are inadequate for qualitative purposes.

The HIARC determined that a MOE of 1000 is required for occupational (there are no residential uses) exposure risk assessments. This includes the conventional 100 and an additional 10 for the use of the use of a LOAEL as well as severity of the effects (marked plasma, RBC and brain cholinesterase inhibition observed at the lowest dose tested).

Since an oral value was selected 100% dermal absorption factor must be used in route-to-route extrapolation for this dermal risk assessment.

This risk assessment is required.

3. Intermediate-Term Dermal (7 Days to Several Months)

Study: Subchronic Toxicity-Rat §82-7

MRID No. 43608201

Executive Summary: See Chronic Dietary

Dose and Endpoint for Risk Assessment: LOAEL=0.2 mg/kg based on plasma cholinesterase inhibition in males and females at the lowest dose tested.

Comments about Study/Endpoint/MOE: **This dose and endpoint replaces the previous dose/endpoint based on the human study.**

The HIARC concluded that the 56-day study in humans (Howard *et al.* 1976) is useful only as *supplemental* data. Although this study used male and female subjects and provided supportive scientific data, it is not appropriate for use in risk assessment since it only included a single dose (thus no dose-response data) and only measured cholinesterase activity in subset of subjects. Therefore, no comparison of dose and effects in animals and human subjects could be made.

The HIARC determined that a MOE of 300 is required for occupational (there are no residential uses) exposure risk assessments. This includes the conventional 100 and 3x for the use of a LOAEL

Since an oral value was selected 100% dermal absorption factor must be used in route-to-route extrapolation for this dermal risk assessment.

This risk assessment is required.

4. Long-Term Dermal (Several Months to Life-Time)

Study: Subchronic Toxicity-Rat §82-7

MRID No. 43608201

Executive Summary: See Chronic Dietary

Dose and Endpoint for Risk Assessment: LOAEL=0.2 mg/kg based on plasma cholinesterase inhibition in males and females at the lowest dose tested.

Comments about Study/Endpoint/MOE: **This dose and endpoint replaces the previous dose/endpoint based on the human study.** The rationale for not using the human study are stated under chronic dietary.

The HIARC determined that a MOE of 300 is required for occupational (there are no residential uses) exposure risk assessments. This includes the conventional 100 and an additional 3x for the use of the use of a LOAEL. According to Subdivision F Guidelines, chronic studies are required only for establishing chronic RfD (i.e., dietary risk assessments). Therefore, the additional factor applied for lack of chronic studies is appropriate for long-term dermal risk assessments.

Since an oral value was selected 100% dermal absorption factor must be used in route-to-route extrapolation for this dermal risk assessment.

This risk assessment is required.

5. Inhalation Exposure (Any Time period)

Except for an acute inhalation toxicity study, the results on which Pirimiphos-methyl is placed in Toxicity Category IV (LC_{50} = >5.04 mg/L), no other studies are available via this route. Therefore, the HIARC selected an oral dose for inhalation risk assessments. Inhalation risk assessments should be as follows:

Step I. The inhalation exposure component (i.e.,µg ai/lbs) using a 100% absorption rate (default value), application rate, number of applications etc. should be converted to an **equivalent oral dose** (mg/kg/day)

Step II. The dermal exposure component (i.e., mg/kg/day) using a 100 % dermal absorption rate should be converted to an **equivalent oral dose**. This dose should then be combined with the converted oral dose in Step I.

Step III The combined dose from Step II should then be compared to the following oral values to calculate the MOE's.

Short-Term	= LOAEL 15 mg/kg/day	MOE = 1000
Intermediate-Term	= LOAEL 0.2 mg/kg/day	MOE = 300
Long-Term	= LOAEL 0.2 mg/kg/day	MOE = 300

This risk assessment is required.

D. Margin of Exposure for Occupational/Exposures

There are no registered residential uses at the present time.

For **Short-Term dermal and inhalation** exposure risk assessments, **a MOE of 1000 is required** and includes the conventional 100 and an additional 10 for the use a LOAEL as well as severity of the effects (marked plasma, RBC and brain cholinesterase inhibition observed at the lowest dose tested).

For **Intermediate and Long-Term dermal and inhalation** exposure risk assessments, **a MOE of 300 is required** and includes the conventional 100 and an additional 3 x factor for the use of a LOAEL (i.e.., lack of a NOEL in the critical study).

E. Aggregate Exposure (Food + Water + Residential) Risk Assessments

Since there are no registered residential uses, aggregate exposure risk assessments will be limited to food plus water.

For **acute** aggregate exposure risk assessment, combine the **high end** exposure values from food plus water and compare it to the acute RfD.

For **chronic** aggregate exposure risk assessment, combine the **average end** exposure values from food plus water and compare it to the chronic RfD.

III. FQPA ASSESSMENT

The FQPA Safety Factor Committee met on June 15 and 16, 1998 to evaluate the hazard and exposure data for pirimiphos methyl and recommend application of the FQPA Safety Factor (as required by Food Quality Protection Act of August 3, 1996), to ensure the protection of infants and children from exposure to these pesticides.

The FQPA Safety Factor Committee has determined that a 3x FQPA safety factor is required for the protection of infants and children from acute and chronic dietary exposure to pirimiphos methyl. For details, refer to the FQPA Safety Committee Report dated August 6, 1998.

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IV. ACUTE TOXICITY

Guideline No.	Study Type	MRID No.	Results	Toxicity Category
81-1	Acute Oral - Rat	00126257	LD_{50} = >2400 mg/kg	III
81-2	Acute Dermal - Rabbit	00126257	LD_{50} =2.6 - 4.05 g/kg (M) >4.05 g/kg (F)	III
81-3	Acute Inhalation-Rat	41556304	LC_{50} = > 5.04 mg/L	II
81-4	Primary Eye Irritation-Rabbit	00126257	Irritant	III
81-5	Primary Skin Irritation-Rabbit	00126257	Irritant	
81-6	Dermal Sensitization-	00126257	--	NA
81-8	Acute Neurotoxicity-Rat	43594101	LOAEL = 15 mg/kg based on cholinesterase inhibition	N/A

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V. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected and Margins of Exposures for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY	MOE
Acute Dietary	LOAEL=15 UF = 1000	Marked plasma, RBC and brain cholinesterase inhibition at the lowest dose tested	Acute Neurotoxicity-Rat Study	Not Relevant
	Acute RfD =0.015 mg/kg/day			
Chronic Dietary	LOAEL=0.2 UF= 1000	Plasma cholinesterase inhibition in both sexes at the lowest dose tested.	Subchronic-Rat	Not Relevant
	Chronic RfD =0.0002 mg/kg/day			
Dermal Absorption	100% ,based upon the comparisons of LOAELs in the oral developmental toxicity (24 mg/kg/day) and the 21-day dermal (4 mg/kg/day) toxicity studies in rabbits based on the common endpoint (cholinesterase inhibition)			
Short-Term (Dermal & Inhalation) [a]	Oral LOAEL=15	Marked plasma, RBC and brain cholinesterase inhibition at the lowest dose tested	Acute Neurotoxicity-Rat Study	1000 [b]
Intermediate-Term (Dermal & Inhalation) [a]	Oral LOAEL=0.2	Plasma cholinesterase inhibition in both sexes at the lowest dose tested.	Subchronic-Rat	300 [c]
Long-Term (Dermal & Inhalation) [a]	Oral LOAEL=0.2	Plasma cholinesterase inhibition in both sexes at the lowest dose tested.	Subchronic-Rat	300 [c]

[a] = Oral values were selected, therefore route-to-route extrapolation is used (100% dermal and 100% inhalation absorption).

[b] = MOE of 1000 due to severity of the effects (marked plasma, RBC and brain ChEI at the LOAEL)

[c] = MOE of 300 due to the use of the LOAEL

MOEs are for occupational exposure risk assessments; there are no registered residential uses at the present time.